Draft Questions for Panel

1. According to 21 CFR 860.7(d)(1), "there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use." In addition, according to 21 CFR 860.7(e)(1), "there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

    a. Please address the following questions regarding the risks to health posed by MMM allograft heart valves:

        i. FDA has identified the following risks to health for MMM allograft heart valves based upon literature and the Manufacturer and User facility Device Experience (MAUDE) database:

            - Death
            - Stroke
            - Heart failure
            - Myocardial infarction
            - Hemorrhage
            - Endocarditis
            - Infection
            - Cardiac arrhythmia
            - Conduction system defect
            - Valve stenosis
            - Transvalvular regurgitation
            - Perivalvular leak
            - Structural valve deterioration
            - Nonstructural dysfunction
            - Hemolysis
            - Valve thrombus
            - Thromboembolism
            - Renal insufficiency or failure
            - Allosensitization, rejection, other immune responses
            - Reoperation
            - Explantation

            Please comment on whether you agree with inclusion of all of these risks in the overall risk assessment of MMM allograft heart valves. In addition, please

comment on whether you believe that any additional risks should be included in the overall risk assessment of MMM allograft heart valves.

ii. Given the available information, please comment on whether there is a reasonable assurance of safety for MMM allograft heart valves.

b. Given the limited availability of clinical data, as well as the limitations of those data (e.g., only 1 cleared MMM allograft heart valve, no randomized control studies, and small patient numbers), it is challenging to draw conclusions regarding the effectiveness of MMM allograft heart valves, particularly regarding their long-term performance, immunogenicity, and potential for recellularization and/or host adaptation. Please comment on whether there is a reasonable assurance of effectiveness for MMM allograft heart valves.

2. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

- insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, AND

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND

- there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness

OR

- insufficient information exists to:
  - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or
  - establish special controls to provide such assurance

BUT

I. is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and

II. does not present a potential unreasonable risk of illness or injury.

Please discuss the following questions:

a. FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of MMM allograft heart valves. Given the limited information available for use of MMM allograft heart valves, FDA does not believe that special controls can be established to mitigate the known risks to health associated with these devices. Do you agree with this assessment?

b. MMM allograft heart valves are life-supporting, life-sustaining devices with significant potential risks of illness or injury. A long history of clinical use of prosthetic heart valves has established numerous known risks to health, including death, valve thrombosis, thromboembolism (including stroke), myocardial infarction, cardiac arrhythmia, hemorrhage, endocarditis, valve stenosis, valve regurgitation, perivalvular leak, and others. Particular risks due to the nature of the MMM allograft valve and its processing include infection (non-sterile devices) and allosensitization. In addition, due to the novelty of MMM processing, isolated literature reports indicate the possibility for increased risks of structural valve deterioration, aneurismal degeneration (of conduit portion), thrombus, thromboembolism, stroke, and renal insufficiency or failure. Do you agree with this assessment? If not, please explain why.

   If you disagree with this assessment, please identify the valid scientific evidence available in support of a reasonable assurance of safety and effectiveness of MMM allograft heart valves when intended for use in heart valve replacement procedures. In addition, please identify the special controls that could be established that you believe would be sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness of MMM allograft heart valves intended for use in heart valve replacement procedures.

In accordance with 21 CFR 860.93, if you recommend a classification other than class III for this device, please discuss the reasons for your recommendation.